UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,633	07/10/2001	Robert John Macleod Wilson	117-347	5975

7590 01/14/2002

Nixon & Vanderhye
1100 North Glebe Road 8th Floor
Arlington, VA 22201

EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1633	11

DATE MAILED: 01/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,633	WILSON ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 12-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 12-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Claims 1-11 have been canceled, as requested. Claims 12-19 are pending in the application.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 12, 13, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 12 is drawn to a method of identifying compounds that inhibit the growth of an organism. The method of claim 12 involves contacting a test compound with the *ycf 24* gene product and determining whether the test compound inhibits the activity of or binds to the product, any such binding or inhibition being indicative that the test compound inhibits the growth of the organism.

Claim 12 is not enabled because it is drawn to a method of identifying compounds that inhibit growth of an organism. However, the method steps involve contacting the test compound

with the *ycf 24* gene product and assaying for binding **OR** inhibition. The mere fact that a test compound could bind to a gene product is not indicative that the compound would inhibit growth of the organism. Therefore, a compound that binds to the *ycf 24* "gene product" would not necessarily be an inhibitor of growth because there is no correlation between binding to the *ycf 24* "gene product" and inhibition of growth. Claim 13 depends on claim 12, and is therefore rejected for the same reason.

Claims 16-19 are drawn to a pharmaceutical composition comprising an inhibitor of *ycf 24* gene product expression and/or activity and a pharmaceutically acceptable carrier or diluent, and a method of preventing or treating infection comprising administering to a patient an inhibitor of *ycf 24* gene product or expression and/or activity. However, the claims are not enabled because specification does not disclose any successful prevention/treatment of symptoms of a disease or disorder, and because the practice of gene therapy is very unpredictable, as discussed below. Therefore one of ordinary skill in the art would not know from the disclosure of the specification how to successfully treat/prevent a disease, such as malaria, with a reasonable expectation of success.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states at page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of identifying compounds that inhibit the growth of an organism (claims 12-15), a pharmaceutical composition comprising an inhibitor of *ycf 24* gene product expression and/or activity (claims 16 and 17), and a method of preventing or treating infection by administering an inhibitor of *ycf 24* gene product expression and/or activity (claims 18 and 19). As written, the claims encompass a pharmaceutical composition comprising an inhibitor and a method of treatment or prevention using the pharmaceutical composition wherein the pharmaceutical composition comprises a nucleic acid; therefore, the nature of the invention is gene therapy. Furthermore, the invention is in a class of invention which the CAFC has characterized as, "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The breadth of the claims is very broad. For instance, the term "gene product" is a broad term that encompasses many materially different elements of the *ycf 24* gene, including the open reading frame, the immature form of mRNA encoded by the *ycf 24* gene, the mature form of the mRNA, the polypeptide encoded by the *ycf 24* gene, all possible allelic variations and splice variants. Compounds that would bind to the "gene product" include factors involved in the replication of the gene, factors involved in the transcription and translation of the gene, and factors that act as agonists or antagonists. Claims 16-19 encompass a pharmaceutical composition comprising an inhibitor of growth. As written, the composition could comprise *any* inhibitor of growth. Additionally, the claims are broad because they are drawn to a method for gene therapy in any host.

Quantity of Experimentation

The quantity of experimentation in this area, particularly with regard to the treatment claims such as claims 18 and 19, is extremely large since determination of the efficacy of these inhibitors would require, initially, in vitro studies to demonstrate proof of principle. That is, prior to any therapeutic intervention, it would be necessary to create a therapeutic vector or naked nucleic acid which could efficiently deliver a sufficient quantity of the therapeutic nucleic acid to the target cells and show that this treatment would have some therapeutic effect on the cells, a series of showings not present in the specification. Following such experimentation, animal models would need to be characterized (an inventive, unpredictable and difficult undertaking in itself) and efficacy would need to be demonstrated in such animal models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of efficient delivery that would provide the nucleic acid sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples (see page 409, first col.). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg.

239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

Furthermore, it is recognized in the art that successful gene therapy treatment in one species is not a reliable indicator that the same treatment will be effective in another species. For instance, Crystal (1995) teaches, "Humans are not simply large mice", and points out that, "predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (see pg 409, col. 1-2). Therefore, results obtained in one species cannot be extrapolated to other species with a reasonable expectation of success.

The method claims 12 and 13 involve contacting the test compound with the *ycf 24* gene product and assaying for binding or inhibition. The mere fact that a test compound could bind to a gene product is not indicative that the compound would inhibit growth of the organism. There are many known factors that bind to "gene products" and do not function as growth inhibitors, for instance Growth Hormone (GH). GH is well known to bind to "gene products" activate and increase growth of eukaryotic cells. Therefore, a compound that binds to the *ycf 24* "gene product" would not necessarily be an inhibitor of growth because there is no correlation between binding to the *ycf 24* "gene product" and inhibition of growth.

Working Examples and Guidance in the Specification

The specification is only prophetic and does not disclose evidence that administration of a nucleic acid results in prevention or alleviation of symptoms of a disease or disorder such as malaria. Furthermore, the specification does not provide any guidance in the specification

towards a specific protocol for administering the gene therapy agent to a subject in such a way that it would avoid the many technical obstacles to gene therapy recognized in the art, as described. The specification does disclose a broad range (1μg-10mg) for administration of naked polynucleotides (see page 19, lines 1-10 of the specification) and for administration of viral vectors (10^4-10^8 pfu, preferably 10^6 pfu for herpes viral vectors; and 10^6-10^{10} pfu, preferably 10^8 pfu for adenoviral vectors); however, these guidelines are only possible dosages that may be effective. The specification does not disclose that administration of the vectors or naked polynucleotides at the concentrations disclosed actually prevents or alleviates symptoms of a disease or disorder in any host. The specification also discloses that the antisense nucleic acids can be used as growth inhibitors (See page 12 of the specification) and discloses possible guidance for administrating the antisense nucleic acid. However, the exact sequence of the antisense nucleic acid, or the length of the antisense polynucleotide sufficient to act as a functional inhibitor is not disclosed. Additionally, there are no examples that the antisense polynucleotides can be administered in such a way to act as a effective therapy. The issues mentioned above regarding the effective delivery of nucleic acids to target cells is applicable to antisense polynucleotides. Furthermore, the specification does not disclose how to administer the vectors or naked polynucleotides (including antisense polynucleotides) in such a way to avoid the many technical obstacles recognized in the art, as described. Without such guidance and the lack of correlative working examples, the claims require additional experimentation without a predictable degree of success on the part of the skilled artisan. The additional experimentation required is deemed to be an undue amount.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

The method of identifying compounds that inhibit growth of an organism is not enabled because the method involves contacting a compound of interest with the *ycf 24* gene product and assaying for binding **OR** inhibition [emphasis added]. The mere fact that a compound could bind to the *ycf 24* gene product is not indicative that the compound would inhibit growth of an organism. A compound that binds to the *ycf 24* "gene product" would not necessarily be an inhibitor of growth because there is no correlation between binding to the *ycf 24* "gene product" and inhibition of growth. Additionally, the Invention as it pertains to gene therapy and a pharmaceutical composition for use in gene therapy is not enabled because, as mentioned above, the level of unpredictability in the art is high, the specification provides no guidance that leads one to a reliable method of treatment. Furthermore, the specification does not provide guidance to overcome art recognized problems in gene therapy required to actually use inhibitors of *ycf 24* gene expression and/or activity as broadly claimed (i.e., encompassing gene therapy in any host). Thus given the broad claims in an art whose nature is identified a unpredictable, the unpredictability of that art, the large amount of experimentation required to overcome the unpredictable barriers, the lack of guidance in the specification, the absence of working examples and the negative teachings in the prior art balanced against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make and/or use the claimed invention as broadly written.

3. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that:

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Claims 14 and 15 are drawn to a method of identifying compounds that inhibit growth of an organism. The method involves contacting a test compound with a test construct comprising a *ycf 24* promoter operably linked to a coding sequence and determining whether the test

compound inhibits expression driven by the promoter, any such inhibition of expression being indicative that the compound inhibits the growth of the organism. However, the specification does not disclose the *ycf 24* promoter in a way to reasonably convey to one skilled in the art that Applicants had identified and were in possession of the *ycf 24* promoter at the time the application was filed. The *ycf 24* promoter is a critical element required for the practice of the claimed method. Promoters are regions of DNA associated with a gene and involved in regulating the expression of the associated gene. Promoters can be located upstream, downstream, or internal to a gene, and can be more than 1000 bases (1kb) from the start site of the gene. Therefore, without sufficient identification of the *ycf 24* promoter, further experimentation would be required for one of ordinary skill in the art to identify the *ycf 24* promoter and to be able to practice the claimed method.

In the application at the time of filing, there is no record or description which would demonstrate conception of any functional promoters associated with the expression of the *ycf 24* gene product. Therefore, the claims fail to meet the written description requirement by encompassing promoter elements which are not described in the specification.

Claims 16-19 are drawn to a pharmaceutical composition comprising an inhibitor of *ycf 24* gene product expression and/or activity and a pharmaceutically acceptable carrier or diluent, and a method of preventing or treating infection comprising administering to a patient an inhibitor of *ycf 24* gene product or expression and/or activity. However, the specification does not sufficiently disclose a functional inhibitor of *ycf 24* expression and/or activity in a way to reasonably convey to one of skill in the art that Applicants had identified and were in possession of a functional inhibitor at the time of filing. The specification only prophetically discloses that

the antisense form of the *ycf 24* gene can be used as an inhibitor. The specification does not disclose evidence that the antisense form of the *ycf 24* gene is a functional inhibitor of gene expression or translation. Also, the specification does not disclose any evidence that antisense polynucleotides are effective at preventing or treating symptoms of a disease or disorder such as malaria, or offer guidance on how to overcome the obstacles to successful therapy recognized in the art, as previously mentioned. Without sufficient disclosure in the specification of an inhibitor that can successfully treat/prevent a disease, one of ordinary skill in the art would not be able to make and/or use an inhibitor of *ycf 24* expression and/or activity with a reasonable expectation of success without undue experimentation.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites, "A method of treating or preventing infection by an organism comprising the *ycf 24* gene in a patient..." This phrase renders the claim indefinite because it is unclear if the organism contains the *ycf 24* gene and the organism is in the patient, or if the *ycf 24* gene is in the patient, or if the method comprises the *ycf 24* gene in a patient. Amendment of the claim to remove the ambiguity is required. Claim 19 depends on claim 18 and is rejected for the same reason.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). For instance, see page 20, lines 3-5 and page 21 lines 2-4 of the specification. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given ONE MONTH from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 16 and 17 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention.

The instant claims are drawn to a pharmaceutical composition comprising an inhibitor of the *ycf 24* gene product expression and/or activity and a pharmaceutical acceptable carrier or diluent (claim 16), wherein the inhibitor is an inhibitor of the growth of the a malaria parasite (claim 17). The claims encompass anything that would function of an inhibitor present in a pharmaceutical acceptable diluent. Laurel Sulfate (SDS) is an example of an inhibitor that could be dissolved in water or PBS, which are pharmaceutically acceptable diluents, and would inhibit the growth of a malaria parasite (and also inhibit the expression and/or translation of the *ycf 24* gene product) by its inherent nature. SDS was available for sale in the United States in 1997 (see SIGMA Catalog, 1997; page 641).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Clark can be reached on (703) 305-4051. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
January 10, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER